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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/883,489	06/19/2001	Jane Theaker	P 0274397 70237-1P US	8685

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EXAMINER

SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 09/19/2002

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/883,489

Applicant(s)

THEAKER ET AL.

Examiner

Jehanne Souaya

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 5 is/are rejected.
- 7) ☒ Claim(s) 4 and 6-8 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

Specification

1. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to the drawings, each of the lettered items should appear in upper case, without underling or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

- (a) Title of the Invention.
- (b) Cross-Reference to Related Applications.
- © Statement Regarding Federally Sponsored Research or Development.
- (d) Reference to a "Sequence Listing," a table, or a computer program listing appendix submitted on compact disc (see 37 CFR 1.52(e)(5)).
- (e) Background of the Invention.
 - 1. Field of the Invention.
 - 2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
- (f) Brief Summary of the Invention.
- (g) Brief Description of the Several Views of the Drawing(s).
- (h) Detailed Description of the Invention.
- (I) Claim or Claims (commencing on a separate sheet).
- (j) Abstract of the Disclosure (commencing on a separate sheet).
- (k) Drawings.
- (l) Sequence Listing, if on paper (see 37 CFR 1.821-1.825).

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Claim Objections

2. Claims 4 and 6-8 are objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim can depend on more than one claim only in the alternative (claims 4, 6, and 8), and a multiple dependent claim cannot depend on another multiple dependent claim (claims 6 and 8). In addition, the claim dependent (claim 7) on an improperly multiple dependent claim cannot be understood. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 2 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 2 is indefinite as it is unclear if the target complementary sequence is part of the probe or if the sequence is part of another nucleic acid.

B) Claim 5 lacks sufficient antecedent basis for the recitation of “the alkyl group” as no alkyl group has been recited in any of the claims to which claim 5 depends from.

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5. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: nucleotide arm sequences on either side (at the 5' and 3' end) of a nucleotide sequence within the probe that is complementary to a target sequence, wherein the nucleotide arm sequences are complementary to each other so that upon hybridization to each other, a stem forms. The specification teaches that the invention relates to improvements of nucleic acid probes known as molecular beacons (see p. 1). The specification teaches that the secondary structure of the probe is key (see line 8) and such secondary structure could not be present if the probe of claim 1 did not contain complementary arm sequences on either side of the region that recognizes the target, such that a stem forms, bringing in close proximity the labeled ends of the probe.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kean et al (Nucleic Acids Research, vol. 22, pp 4497-4503, 1994).

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The claim is directed to an oligonucleotide that contains 2'-O-substituted RNA wherein the oligonucleotide has donor and acceptor species attached at or near its termini. The following rejection is directed to the embodiment that "donor and acceptor species" are fluorophores. Kean teaches a 2'-O-methyl substituted ribonucleotide (table 1, #3, p. 4499). It is noted that the claim does not specify what type of "donor and acceptor species" are "attached" at or near the ends of the oligonucleotide, thus the term has been broadly interpreted to encompass phosphate and hydroxy groups that are inherently present at either end of the oligonucleotide which are involved in the polymerization of additional nucleotides to the oligonucleotide taught by Kean.

8. Claims 1-3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Kool (US Patent 5,514,546, 5/7/1996).

The claims are directed to an oligonucleotide that contains 2'-O-substituted RNA where the oligonucleotide has donor and acceptor species attached at or near its termini, a stem duplex consisting of nucleotide sequences 5' and 3' to a target complementary sequence, wherein the stem duplex is of 3-6 bases in length, and wherein the substituent is a methyl group. Kool teaches a probe comprising a stem loop structure (see figure 1, col. 5, line 53), wherein the stem domain is at least about 2 base pairs in length, and wherein the stem domain is preferably about 3, and especially preferably about 6 base pairs (col. 6, lines 49-53). Kool further teaches that the probe can be DNA or RNA and can contain nucleotide analogs, especially preferred are nucleotides with 2'-O-methyl ribose moiety (see col. 13, lines 11-20, and lines 44-46). Kool

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further teaches that the stem-loop probe includes donor and acceptor fluorophores on each end of the oligonucleotides (see col. 26, lines 41-46, and 63-67).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-3 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al (Nature Biotechnology, 1996, vol. 14, pp 303-308, hereinafter referred to as Tyagi I) in view of Kean et al (Nucleic Acids Research, vol. 22, pp 4497-4503), and further in view of Inoue et al

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(Nucleic Acids Research, 1987, vol. 15, pp 6131-6148), and Tyagi et al (WO 95/13399, May 18, 1999, hereinafter referred to as Tyagi II).

The claims are drawn to nuclease resistant 2'-O-substituted RNA probes with donor and acceptor species attached at or near their termini. The following rejection is directed to the embodiment that "donor and acceptor species" are fluorophores. Tyagi I teaches nucleic acid probes that recognize and report the presence of specific nucleic acids in homogenous solutions (see abstract). Tyagi I teaches that the probes possess a stem and loop structure (p. 303, col. 1 and Fig 1). Tyagi I teaches that the loop portion of the molecule is a probe sequence which is complementary to a predetermined sequence in a target nucleic acid and that the stem is formed by the annealing of two complementary arm sequences that are on either side of the probe sequence. Tyagi I teaches that a florescent moiety is attaches to the end of one arm and a non fluorescent quenching moiety is attached to the end of the other arm of the probe (col.1, p 303, para 2). Tyagi I teaches that the stem keeps these two moieties in close proximity to each other, causing the fluorescence of the fluorophore to be quenched by fluorescence energy transfer. Tyagi I teaches that when the probe encounters a target molecule, it forms a hybrid that is longer and more stable than the hybrid formed by the arm sequences, and thus the probe undergoes a spontaneous conformational change that forces the arm sequences apart and causes the fluorophore and quencher to move away form each other, thereby allowing the fluorophore to fluoresce when illuminated by ultraviolet light (see bridging para of cols 1 an 2 p. 303) (claims 1-3). While the molecular beacon probe taught by Tyagi I in figure 2 possesses 5 nucleotides in the

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stem, Tyagi teaches that arm sequences (that form the stem) of about 4 to 12 nucleotides form stable stem hybrids, yet they are sufficiently short to dissociate when the probe hybridizes to its target (see p. 307, col 1, first paragraph in “discussion”). Therefore, in constructing probes as taught by Tyagi I, the ordinary artisan would have been taught that the most significant design parameters that affect the conformation change (needed for detection) are the length of the arm sequences and the length of the probe sequence and would further have been taught that probes with stems of “about 4 to 12 nucleotides” (fully encompasses 3-6 bases as claimed in claim 3) were observed by Tyagi to perform sufficiently as needed. Furthermore, it would have been obvious that probes with stem lengths as short as 3 bases could be used in constructing a probe as taught by Tyagi I because Tyagi II teaches (see p. 23, middle of first full para) that 3-25 nucleotide arm lengths (form the stem) can perform the function of keeping the arms associated when the probe (same probe design as taught by Tyagi I) is not bound to the target.

The limitations of claim 1 regarding a 2'-O-substituted RNA and claim 5 regarding a methyl substituent are not specifically taught by Tyagi. With regard to 2'-O-methyl substituted RNA, it would have been prima facie obvious to modify the probes of Tyagi with 2'-O-methyl ribose sugars because Kean teaches that such probes have improved binding constants (see abstract and p. 4497, col. 2, para 2) and that oligo-2'-O-methylribonucleotide/RNA duplexes have greater stability than oligodeoxyribonucleotide/RNA duplexes. Therefore, if the ordinary artisan were to want to use the probes as taught by Tyagi to detect an RNA target sequence (see abstract of Tyagi I), for example to detect RNA expression, the ordinary artisan would have been

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taught by Kean that oligo-2'-O- methylribonucleotide probes would form more stable duplexes than an oligodeoxyribonucleotide probe. The ordinary artisan would have further been motivated to construct 2'-O-methyl substituted RNA probes because Tyagi I teaches that it may be necessary to modify the nucleotides or internucleotide bonds of the probe to provide protection from endonucleases (p. 307, col. 2, para 5). Inoue specifically teaches that 2'-O-methyl ribonucleosides in probes are resistant to digestion by nucleolytic enzymes (p. 6132, para 2). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the probes taught by Tyagi with the 2'-O-substituted methyl ribonucleotides of Inoue because Inoue teaches that these substituted probes are resistant to nucleases. The ordinary artisan would have been motivated to modify the probes of Tyagi as Tyagi teaches a need for such modifications in discussing the necessity of providing probes with protection against endonucleases.

11. No claims are allowable over the cited prior art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
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Sept. 12, 2002